Clinical Infectious Diseases

MAJOR ARTICLE

Human Papillomavirus Vaccination Prior to Loop Electroexcision Procedure Does Not Prevent Recurrent Cervical High-grade Squamous Intraepithelial Lesions in Women Living With Human Immunodeficiency Virus: A Randomized, Double-blind, Placebo-controlled Trial

Cynthia Firnhaber,[1,2] Avril Swarts,[2] Vuyokazi Jezile,[2] Masango Mulongo,[2] Bridgette Goeieman,[3] Sophie Williams,[3] Mark Faesen,[3] Pamela Michelow,[4,5] and Timothy Wilkin[6]

[1]Division of Infectious Disease, Department of Medicine, University of Colorado Medical School, Aurora, Colorado, USA, [2]Clinical HIV Research Unit, Department of Clinical Medicine, University of the Witwatersrand, Johannesburg, South Africa, [3]Right to Care Helen Joseph Hospital, Johannesburg, South Africa, [4]Department of Anatomical Pathology, University of the Witwatersrand, Johannesburg, South Africa, [5]National Health Laboratory Service, Johannesburg, South Africa, and [6]Division of Infectious Diseases, Weill Cornell Medical College, New York, New York, USA

Background. Women living with human immunodeficiency virus (HIV), especially in sub-Saharan Africa, are at high risk for cervical high-grade squamous intraepithelial lesions (HSIL) and cervical cancer. These women have high HSIL recurrence rates after loop electroexcision procedure (LEEP). Retrospective studies suggest that human papillomavirus (HPV) vaccination improves response to treatment of cervical HSIL.

Methods. We performed a double-blind, randomized clinical trial enrolling 180 women living with HIV in Johannesburg, South Africa, diagnosed with cervical HSIL by colposcopic biopsy. Women received quadrivalent HPV vaccine or placebo (1:1) at entry, week 4, and week 26. LEEP was performed at week 4. Colposcopic-directed biopsies and cervical cytology were performed at weeks 26 and 52. The primary endpoint, cervical HSIL by histology or cytology at either week 26 or 52, was compared between arms using χ^2 analysis.

Results. Participant characteristics included median age of 39 years and median CD4 count 489 cells/μL, and 94% had HIV suppression. One hundred seventy-four women completed the vaccine/placebo series and had evaluable results at week 26 or 52. The proportion experiencing the primary endpoint was similar in the vaccine and placebo groups (53% vs 45%; relative risk, 1.18 [95% confidence interval, .87–1.6]; $P = .29$). HSIL recurrence was associated with a LEEP biopsy result of HSIL and detection of HSIL at the margins of the LEEP sample.

Conclusions. This study did not support HPV vaccination to prevent recurrent HSIL after LEEP in women living with HIV. Recurrent HSIL was high despite virologic suppression. Improved treatments are needed for HSIL to reduce the burden of cervical cancer among women living with HIV.

Clinical Trials Registration. NCT01928225.

Keywords. HIV positive women; HSIL; LEEP; HPV vaccine.

Cervical cancer is one of the most common cancers in women in sub-Saharan Africa. The most recent compilation of global data indicates that an estimated 570 000 new cases of cervical cancer occur annually among women worldwide and nearly 80% of these are in developing countries, where screening programs are not well established. It is estimated that 311 000 women died in 2018 from cervical cancer. Worldwide, cervical cancer accounts for 7.5% of all female cancer deaths; most occur in low middle-income countries [1]. Women living with human immunodeficiency virus (HIV) have high rates of cervical high-grade squamous intraepithelial lesions (HSIL), especially in low- and middle-income countries [2, 3]. One study in an HIV clinic in Johannesburg showed rates of cervical cancer in an HIV treatment clinic of 260 per 100 000 after a screening program had been implemented. This was down from the significant rates of 615 per 100 000 before a screening program was developed [4]. Cervical cancer rates are much lower in the general population of South African women (22.8–27 per 100 000) compared with South African women living with HIV [5].

Cervical HSIL, also known as cervical intraepithelial neoplasia (CIN) grade 2 or 3, the precursor lesion to cervical cancer, is treated by either ablative or excisional methods. A very efficient and effective outpatient procedure requiring only local anesthesia is loop electrosurgical excision procedure (LEEP)/

Received 11 June 2020; editorial decision 16 September 2020; published online 25 September 2020.

Correspondence: C. S. Firnhaber, University of Colorado Anschutz Medical Campus, 13001 E 17th Place, Aurora, CO 80045 (cynthia.firnhaber@cuanschutz.edu).

Clinical Infectious Diseases® 2021;73(7):e2211–6

DOI: 10.1093/cid/ciaa1456

large loop excision of the transformation zone (LLETZ). Rates of treatment failure, defined as incomplete excision of dysplasia from the ectocervical and/or endocervical margins on pathology specimens, are between 10% and 15% for the LEEP/LLETZ procedure in immunocompetent women [6].

Women living with HIV often have larger lesions or multifocal lesions resulting in incomplete removal of HSIL [7]. Up to 50% of women living with HIV treated with LEEP had persistent or recurrent HSIL [8]. A randomized study in South African women living with HIV that compared LEEP vs cryotherapy treatment of cervical HSIL found persistent or recurrent HSIL in 19% and 28%, respectively, 1 year later [9].

With improved access to antiretroviral therapy (ART), women living with HIV are living longer, allowing time for persistent high-risk human papillomavirus (HPV) infections and HSIL to progress to invasive cancer [10]. Poor HSIL treatment outcomes may compromise the effectiveness of cervical cancer control programs. The additional follow-up and repeated treatments represent a challenge for programs with limited resources and capacity.

There have been several nonrandomized or post hoc analyses suggesting that adjunctive HPV vaccination improves HSIL outcomes in HIV-uninfected women undergoing LEEP [11–13]. This trial was conducted to test the hypothesis that HPV vaccination will reduce the occurrence of cervical HSIL post-LEEP in women living with HIV.

METHODS

Study Design and Participants

This trial was a randomized, double-blinded, placebo-controlled, phase 3 trial conducted at a single site in Johannesburg. The protocol was designed to enroll 180 women living with HIV with 1 year of follow-up. The protocol was reviewed and approved by the Human Ethics Committee (Medical) of the University of the Witwatersrand (ethics number 131101) and registered with ClinicalTrials.gov (NCT01928225).

Entry Criteria

Participants met the following criteria: HIV type 1 (HIV-1) infection; age 18 years or older; HSIL on cervical histology; not pregnant; and utilizing contraception if sexually active. Women were excluded for a prior history of invasive or microinvasive cervical, vaginal, vulvar, or anal cancer; prior hysterectomy; cervical treatments within 1 year prior to study; cervical, vaginal, or vulvar lesions suspicious for cancer; prior HPV vaccination; receipt of anticoagulants; known sensitivity to vaccine components; hemophilia or bleeding diathesis; use of antineoplastic or immunomodulatory treatment; breastfeeding; and <3 months postpartum.

Randomization and Masking

Participants were randomly assigned 1:1 to either quadrivalent (types 6, 11, 16, and 18) HPV vaccine (4vHPV; Merck and Co, Inc, Kenilworth, New Jersey) or placebo at baseline, week 4, and week 26. The placebo was 0.9% sodium chloride. Vaccine or placebo was administered by unblinded pharmacists who shielded the participant from viewing the syringe, as only prefilled 4vHPV syringes were available for this trial. Blocked randomization with a block size of 10 was used to determine the randomization sequence, and the randomization list was maintained by study pharmacists. Participants and all study personnel besides pharmacists remained blinded to vaccine assignment.

This study used a modified schedule where the second vaccine is given at 4 weeks instead of 8 weeks. This alternative regimen is acceptable according to the Advisory Committee on Immunization Practices, which sets the standard for United States immunization practices and is preferred by Merck for use in this study [14]. This schedule was chosen to minimize the time between diagnosis of HSIL and LEEP.

Study Procedures

Potential participants were recruited by study staff and focused on women diagnosed with cervical HSIL on histology through routine cervical cancer screening services at the Themba Lethu (an HIV treatment clinic) in Johannesburg, South Africa. Potential participants provided informed consent. Consent discussions occurred in English, Zulu, or Sesotho.

At the baseline visit, a medical history was obtained through participant interviews to obtain information on sociodemographic characteristics, ART status, and other factors, including smoking and snuff (traditional chewing tobacco) use, reproductive/menstrual characteristics, and history of contraceptive use. Blood was obtained for CD4 cell count and plasma HIV level.

At week 4, participants underwent LEEP treatment to remove cervical HSIL. The LEEP was performed according to International Agency for Research on Cancer or World Health Organization recommendations at the discretion of the treating provider. At weeks 26 and 52, women underwent cervical cytology and cervical colposcopy with biopsy of visible lesions. If no lesions were seen, then 2 biopsies were from 6:00 and 12:00 positions on the cervix. At least 2 biopsies were obtained for all participants. All biopsies were placed in a single container and only 1 pathology result was obtained.

For women of childbearing potential, a urine pregnancy test was obtained at each visit prior to vaccination or cervical procedures. If a woman became pregnant on the study, she was removed from the study and pregnancy outcomes were collected.

Cytology specimens were interpreted using the Bethesda System [15]. Cervical biopsy specimens and LEEP biopsy specimens were classified as no evidence of intraepithelial lesion or malignancy; low-grade squamous intraepithelial lesion (LSIL) (condyloma, CIN1, or atypia); HSIL (CIN2/3 or carcinoma in situ); or invasive cancer. The results were classified according to the most severe pathologic finding. For LEEP specimens with

HSIL detected, the specimen was examined to determine if HSIL was present at the endocervical and ectocervical margin. The specimen was considered margin positive if HSIL was detected at either the endocervical or ectocervical margin.

Quality Assurance

The cytology unit of the Anatomical Pathology Department, National Health Laboratory Service has several internal and external quality assurance (QA) modalities for cervical cytology. Internal QA includes rapid review of all reportedly negative smears, while positive smears (atypical squamous cells of uncertain significance and worse) are seen by 2 trained cytology personnel (1 junior and 1 senior), in addition to cytologic-histologic correlation and retrospective review if there is a discrepancy between the current and previous cervical smear. External QA comprises, inter alia, proficiency testing utilizing the Royal College of Pathologists Quality Assurance Programme and annual inspection by the South African National Accreditation System (SANAS). Study cytology readings have previously undergone quality assurance by the University of North Carolina with 80%–85% concordance of results [16]. Quality assurance in histopathology includes annual SANAS accreditation, proficiency testing using the Royal College of Pathologists Quality Assurance Programme, and clinicopathologic correlation.

Outcomes

The primary endpoint was a composite of HSIL on cervical histology or cytology at week 26 or week 52. Secondary endpoints included cytology results alone, histology results alone, CIN3 on cervical histology, and grade 3 or 4 adverse events related to vaccination. Adverse events were solicited during clinical assessments and graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult Adverse Events, version 1.0, December 2004 [17]. Adverse events related to LEEP or cervical biopsies were graded using the DAIDS Female Genital Grading Table for Use in Microbicide Studies, which can be found on the DAIDS Regulatory Support Center website (http://rsc.tech-res.com/safetyandpharmacovigilance/).

Statistical Analyses

We targeted 80% power to show a reduction of the primary endpoint from 40% in the control group to 20% in the vaccine group using a type 1 error of .05. We inflated the sample size by 22 participants to account for loss to follow-up and missing data. The primary analysis only included women with evaluable cytology or histology specimens at either week 26 or week 52. We used χ^2 analysis to compare outcomes between arms. We used multivariable logistic regression to examine predictors of the primary endpoint. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Protocol Monitoring

A data and safety monitoring board (DSMB) monitored study conduct and safety. The DSMB was constituted specifically for the trial and was comprised of investigators with experience in HPV cancer prevention studies, HPV vaccine studies, and HPV virology. They did not perform an interim efficacy review.

RESULTS

Study Participants

From September 2014 until October 2016, 180 women were enrolled and randomized. Characteristics of study participants are shown in Table 1. The median age of the women enrolled in the study was 39 years, and 98% were black African. The median CD4 count was 489 cells/μL, the median nadir CD4 count was 116 cells/μL, and 94% were virally suppressed

Table 1. Characteristics of Trial Participants

Characteristic	4vHPV Arm (n = 90)	Placebo Arm (n = 90)	Total (N = 180)
Cervical cytology			
ASCUS	2 (2.2)	3 (3.3)	5 (2.8)
ASC-H	8 (8.9)	7 (7.8)	15 (8.3)
LSIL	1 (1.1)	4 (4.4)	5 (2.8)
HSIL	78 (86.7)	76 (84.4)	154 (85.6)
Unsatisfactory	1 (1.1)	0 (0)	1 (.6)
Cervical histology			
CIN2	40 (44)	46 (51)	86 (48)
CIN3	49 (54)	44 (49)	93 (52)
Inadequate	1 (1)	0	1 (1)
Race			
Black	90 (100)	86 (96)	176 (98)
Other	0	3 (3)	3 (2)
White	0	1 (1)	1 (1)
Current tobacco use			
Yes	3 (3)	5 (6)	8 (4)
No	87 (97)	85 (94)	172 (96)
Plasma HIV-1 RNA, copies/mL			
<200	77 (95)	76 (93)	153 (94)
200–1000	1 (1)	1 (1)	2 (1)
>1000	3 (4)	5 (6)	8 (5)
Missing[a]	9	8	17
Age, y, median (IQR)	40.1 (34.8–46.6)	39.1 (35.2–44.2)	39.2 (34.9–45.5)
CD4 count, cells/μL, median (IQR)[b]	511 (300–689)	483 (337–745)	489 (302–724)
Nadir CD4 count, cells/μL, median (IQR)[c]	125 (61–200)	108 (50–200)	116 (50–200)

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: 4vHPV, quadrivalent human papillomavirus vaccine; ASC-H, atypical squamous cells suggestive of high-grade squamous intraepithelial lesion; ASCUS, atypical squamous cells of uncertain significance; CIN, cervical intraepithelial neoplasia; HIV-1, human immunodeficiency virus type 1; HSIL, high-grade squamous intraepithelial lesion; IQR, interquartile range; LSIL, low-grade squamous intraepithelial lesion.

[a]Participants with missing plasma HIV-1 RNA values were excluded from the proportions.

[b]Missing: n = 17.

[c]Missing: n = 2.

with a plasma HIV-1 RNA level <200 copies/mL. ART status was available on 167 of 180 (93%) of the women in the study: 134 (80%) were on a nonnucleoside reverse transcriptase inhibitor and 2 were on a nucleoside reverse transcriptase inhibitor (NRTI); 32 (19%) were on a protease inhibitor and 2 on NRTI; 1 (1%) was not receiving ART. The cervical cytology obtained through standard of care prior to study entry was HSIL or atypical squamous cells suggestive of HSIL (ASC-H) in 93% of women. The histology sample diagnostic of HSIL was interpreted as CIN3 in 52% of women.

Study Conduct

There were 2 randomization errors: 1 woman who was HIV uninfected and 1 woman who was pregnant. Both errors were detected immediately after randomization and the women were withdrawn prior to study vaccination and were replaced. One participant had an unevaluable histology specimen prior to study entry; she was included in the analysis. One woman was unblinded and removed from the trial due to a cervical cancer found on the week 4 LEEP biopsy. She was counted as a failure for the primary endpoint.

Of 180 enrolled in the study, 86% (154/180) completed the 52 weeks of study follow-up. See Figure 1 for participant disposition. LEEP was completed in 179 (99%) women. The vaccine series was completed in 174 (97%) women, and 174 (97%) women were included in the analysis of the primary endpoint. Six participants did not have endpoint data either at week 26 or 52. Five women left the study early due to pregnancy.

LEEP Biopsy Results

Among 179 women who underwent LEEP, 1 woman did not have an evaluable result. HSIL was found in 128 (72%) women; 49 (27%) had LSIL and 1 (0.6%) had no evidence of malignancy or intraepithelial lesion. Of the 128 women who had HSIL on LEEP, 94 (73%) had positive margins for HSIL.

Study Outcomes

Study outcomes are shown in Table 2. The primary endpoint was not significantly different between the vaccine and placebo arms, with cytologic or histologic HSIL found at week 26 or 52 in 46 (53%) and 39 (45%) of women, respectively (relative risk [RR], 1.18 [95% confidence interval {CI}, .87–1.6]; $P = .29$). There was no significant difference between groups when evaluating HSIL by histology only: 28 (32%) vs 27 (31%) (RR, 1.04 [95% CI, .67–1.61]; $P = .8$). Similarly, there was no difference when comparing CIN3: 9 (10%) vs 11 (13%) (RR, 0.82 [95% CI, .36–1.88]; $P = .64$). Similar results were found when examining cytology or histologic HSIL at week 26 only and week 52 only (data not shown).

Predictors of Cervical HSIL on Histology

Age, CD4 cell count, and nadir CD4 count were not related to the detection of HSIL on histology at week 26 or week 52. There were too few women reporting tobacco use or having unsuppressed plasma HIV-1 to assess their relationship to study outcomes. The week 4 LEEP histology result was strongly related to HSIL on histology at week 26 or 52, with this occurring in 7 of 49 (14.3%) women with LSIL or no evidence of intraepithelial lesion LEEP results compared with 48 of 124 (38.7%) women with an HSIL result (odds ratio [OR], 3.79 [95% CI, 1.58–9.12]; $P = .0029$). LEEP margin status was also strongly related to HSIL on histology at week 26 or 52 with this occurring in 39 of 91 (49.9%) women with LEEP margins positive for HSIL compared with 16 of 62 (19.5%) women without this result (OR, 3.1 [95% CI, 1.56–6.14]; $P = .0013$). A multivariable model was not attempted as LEEP margin status and LEEP biopsy result are strongly related.

Safety Data

There were no grade 3 or 4 events related to vaccination. No one discontinued the vaccine series early due to adverse events. One participant was diagnosed with basaloid cervical cancer on week 4 LEEP biopsy. One participant died; this was deemed to be unrelated to vaccine, study treatment, or cervical cancer. The DSMB performed 3 interim reviews and had no significant concerns with participant safety or study conduct.

DISCUSSION

This is the first prospective, double-blind, placebo-controlled randomized study to evaluate whether HPV vaccination improves HSIL outcomes after LEEP in women living with HIV. We found no evidence for a beneficial effect. This lack of benefit was consistent across various supporting analyses. These results are distinct from retrospective or nonrandomized comparisons in HIV-negative women (described below) that have suggested a reduced occurrence of HSIL after cervical treatments in women who received adjuvant HPV vaccine. A post hoc analysis of women diagnosed with cervical HSIL during phase 3 trials of 4vHPV found that women who had been vaccinated previously with 4vHPV had a 65% lower risk of HSIL after LEEP compared with women who had received placebo. A retrospective study of LEEP outcomes found a decreased risk of recurrent HSIL in those who had been vaccinated (9/360 [2.5%]) compared with those who were unvaccinated (27/377 [7.2%]) [12]. A similar post hoc analysis of a bivalent HPV vaccine trial found an 88% reduction of HSIL in women who had been vaccinated compared with placebo [13]. A randomized, double-blind, placebo-controlled trial of 4vHPV did not find a benefit on anal HSIL outcomes from vaccination among men and women living with HIV [18].

Our results may have differed for several reasons. First, the retrospective and post hoc nature of these studies limits our ability to infer efficacy as uncontrolled bias may be present. We enrolled women living with HIV. Although these women were generally healthy on effective ART (median CD4 count, 489 cells/μL; 94%

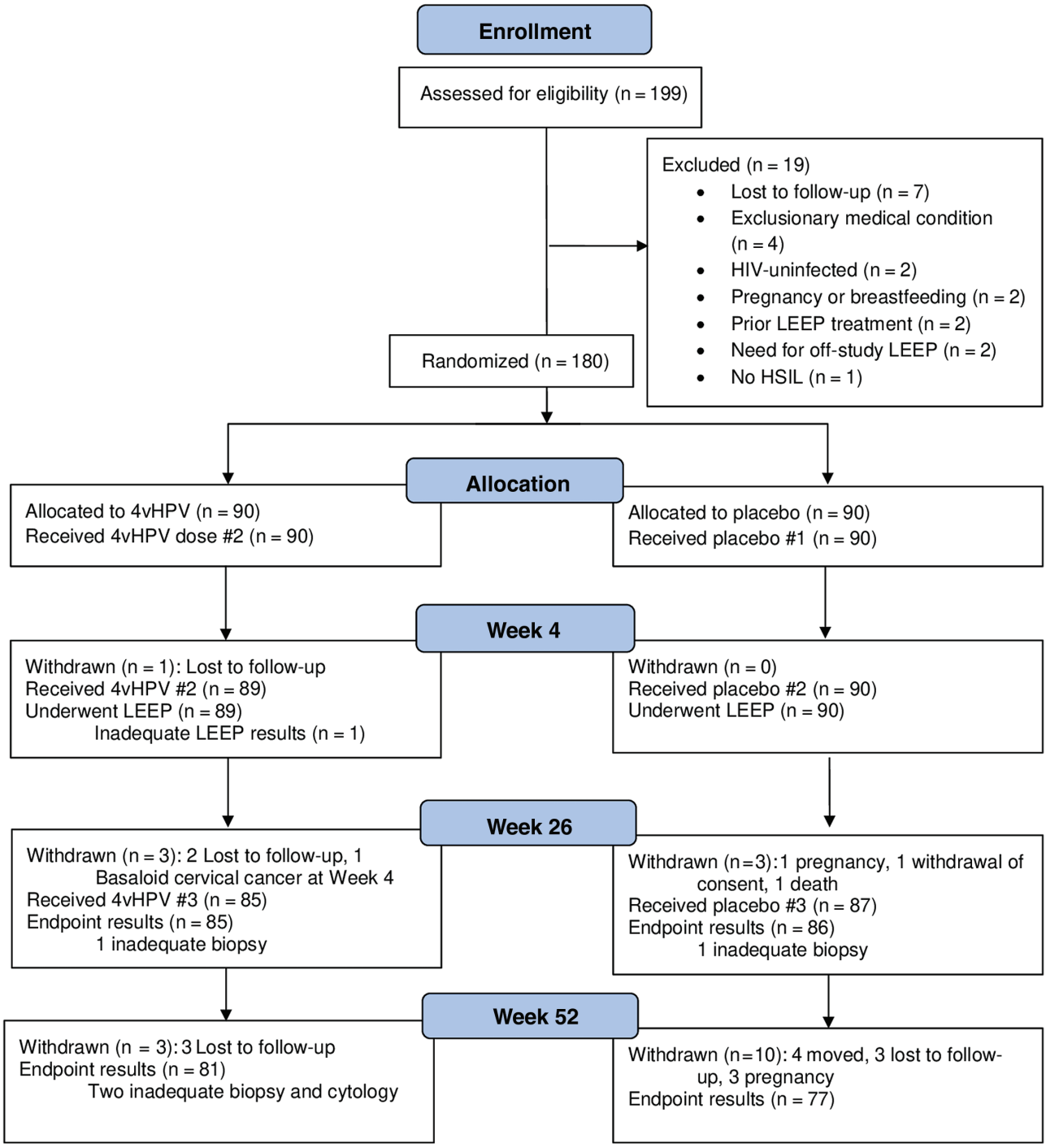

Figure 1. Participant disposition. Abbreviations: 4vHPV, quadrivalent human papillomavirus vaccine; HIV, human immunodeficiency virus; HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electroexcision procedure.

viral suppression), these women had been significantly immunosuppressed before starting ART with a median CD4 nadir of 116 cells/μL. Women living with HIV are more likely to have cervical HSIL caused by nonvaccine HPV types compared with women without HIV [19]. South African guidelines limit colposcopy to women having HSIL, ASC-H, or glandular or persistent LSIL cytology, and the vast majority of women in this trial had cytology results of ASC-H or HSIL, suggesting more severe HSIL. Women living with HIV have larger and more diffuse HSIL lesions than women without HIV, which is more likely to lead to incomplete treatment with positive margins. Positive margins are a risk factor for persistent/recurrent disease [7], and we confirmed this finding

Table 2. High-grade Squamous Intraepithelial Lesion Recurrence

Endpoint	4vHPV (n = 87)	Placebo (n = 87)	RR (95% CI)	*P* Value
Cytologic or histologic HSIL (primary endpoint)	46 (52.9)	39 (44.8)	1.2 (.87–1.6)	.29
Histologic HSIL (CIN2 or CIN3)	28 (32)	27 (31)	1.04 (.67–1.6)	.8
CIN3	9 (10)	11 (13)	.82 (.36–1.9)	.64

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: 4vHPV, quadrivalent human papillomavirus vaccine; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; RR, relative risk.

in our trial. The timing of the vaccine in this study as compared to the studies discussed above may have also explained the differences of our results. The HIV-negative women in these studies completed the vaccine series before the lesions were treated. In our study, we performed the LEEP treatment at the same visit of the administration of the second vaccine dose.

There are several limitations to this study. We did not perform HPV testing in this trial due to lack of resources. HPV testing of cervical swab or histology specimens would allow us to understand whether the lack of efficacy was due to a predominance of nonvaccine HPV types. Another limitation is that we used the quadrivalent HPV vaccine. The 9-valent HPV vaccine may have led to different results. We did not have an adjudicated central pathology panel to determine the endpoint status for participants. It is also possible that possible benefit may have been seen if observing for a longer period of time, as has been seen in other HPV vaccine trials.

This randomized, double-blind, placebo-controlled clinical trial of the quadrivalent HPV vaccine did not provide any evidence for reduced occurrence of HSIL after LEEP treatment. The overall burden of HSIL after LEEP that we observed underscores the urgent need for further research into new treatment options to reduce the risk of cervical cancer for women living with HIV.

Notes

Acknowledgments. In memoriam: Professor Simon Levin, a dedicated clinician and mentor to many in southern Africa.

Financial support. This work was supported by Merck & Co, Inc: Investigator Studies Program grant number 50971 (Merck protocol number V501-190) and the United States Agency for International Development (674-A-00-08-0000).

Potential conflicts of interest. T. W. reports grants and personal fees from GlaxoSmithKline and ViiV Healthcare. C. F. has received travel fees from Merck & Co, Inc. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Global Initiative for Cancer Registry Development. Data visualization tools for exploring the global cancer burden in 2018. Available at: https://gco.iarc.fr/today/home. Accessed 22 August 2020.
2. Massad LS, Xie X, D'Souza G, et al. Incidence of cervical precancers among HIV-seropositive women. Am J Obstet Gynecol **2015**; 212:606.e1–8.
3. Firnhaber C, Mayisela N, Mao L, et al. Validation of cervical cancer screening methods in HIV positive women from Johannesburg, South Africa. PLoS One **2013**; 8:e53494.
4. Rohner E, Sengayi M, Goeieman B, et al. Cervical cancer risk and impact of Pap-based screening in HIV-positive women on antiretroviral therapy in Johannesburg, South Africa. Int J Cancer **2017**; 141:488–96.
5. Western Cape Government. Cervical cancer report. Available at: https://www.westerncape.gov.za/general-publication/cervical-cancer. Accessed 22 August 2020.
6. Cox JT. Management of women with cervical cancer precursor lesions. Obstet Gynecol Clin North Am **2002**; 29:787–816.
7. Debeaudrap P, Sobngwi J, Tebeu PM, Clifford GM. Residual or recurrent precancerous lesions after treatment of cervical lesions in human immunodeficiency virus-infected women: a systematic review and meta-analysis of treatment failure. Clin Infect Dis **2019**; 69:1555–65.
8. Adam Y, van Gelderen CJ, de Bruyn G, McIntyre JA, Turton DA, Martinson NA. Predictors of persistent cytologic abnormalities after treatment of cervical intraepithelial neoplasia in Soweto, South Africa: a cohort study in a HIV high prevalence population. BMC Cancer **2008**; 8:211.
9. Smith JS, Sanusi B, Swarts A, et al. A randomized clinical trial comparing cervical dysplasia treatment with cryotherapy vs loop electrosurgical excision procedure in HIV-seropositive women from Johannesburg, South Africa. Am J Obstet Gynecol **2017**; 217:183.e1–11.
10. Memiah P, Mbuthia W, Kiiru G, et al. Prevalence and risk factors associated with precancerous cervical cancer lesions among HIV-infected women in resource-limited settings. AIDS Res Treat **2012**; 2012:953743.
11. Joura EA, Garland SM, Paavonen J, et al; FUTURE I and II Study Group. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. BMJ **2012**; 344:e1401.
12. Kang WD, Choi HS, Kim SM. Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2-3)? Gynecol Oncol **2013**; 130:264–8.
13. Garland SM, Paavonen J, Jaisamrarn U, et al; HPV PATRICIA Study Group. Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: post-hoc analysis from a randomized controlled trial. Int J Cancer **2016**; 139:2812–26.
14. Markowitz LE, Dunne EF, Saraiya M, et al; Centers for Disease Control and Prevention. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **2014**; 63:1–30.
15. Solomon D. The Bethesda system for reporting cervical cytology: definitions, criteria, and explanatory notes. 3rd ed. New York: Springer, **2015**.
16. Firnhaber C, Zungu K, Levin S, et al. Diverse and high prevalence of human papillomavirus associated with a significant high rate of cervical dysplasia in human immunodeficiency virus-infected women in Johannesburg, South Africa. Acta Cytol **2009**; 53:10–7.
17. US Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS table for grading the severity of adult and pediatric adverse events, version 1.0. **2004** [**updated 2009**]. Available at: http://rsc.tech-res.com/docs/ default-source/safety/table_for_grading_severity_of_adult_pediatric_adverse_ events.pdf. Accessed 22 August 2020.
18. Wilkin TJ, Chen H, Cespedes MS, et al. A randomized, placebo-controlled trial of the quadrivalent human papillomavirus vaccine in human immunodeficiency virus-infected adults aged 27 years or older: AIDS Clinical Trials Group Protocol A5298. Clin Infect Dis **2018**; 67:1339–46.
19. Mbatha JN, Taylor M, Kleppa E, et al. High-risk human papillomavirus types in HIV-infected and HIV-uninfected young women in KwaZulu-Natal, South Africa: implications for vaccination. Infect Dis (Lond) **2017**; 49:601–8.